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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of	:	**Confirmation No. 5439**
Peter POCHLAUER et al.	:	Docket No. 2001-0331A
Serial No.09/834,926	:	Group Art Unit 1623
Filed April 16, 2001	:	Examiner P. Zucker

PROCESS FOR THE PREPARATION OF
OPTICALLY AND CHEMICALLY HIGHLY PURE
(R) - or (S)-a-HYDROXYCARBOXYLIC ACIDS

APPELLANTS' BRIEF

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

This is an appeal from the final rejection of claims 11-14 and 16-23, all of the claims in this application.

No claim stands allowed.

1. REAL PARTY IN INTEREST

The real party in interest is DSM Fine Chemicals Austria Nfg GmbH & Co KG, Linz, Austria.

2. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

3. STATUS OF CLAIMS

The Claims on Appeal Are 11-14 and 16-23.

Claims 1-10 and 15 have been cancelled.

4. STATUS OF AMENDMENTS

No amendment was filed after final rejection and the comment in paragraph 7 of the Advisory Action of December 16, 2002 to the effect that the proposed amendments will not be entered is apparently inadvertent.

5. SUMMARY OF INVENTION

The claims on appeal are directed to a process for increasing the chemical and optical purity of certain (*R*)- and (*S*)-α-hydroxycarboxylic acids as discussed on page 1, line 34 to page 2, line 5 of the present specification.

The process involves recrystallizing certain impure optically active α-hydroxycarboxylic acids which have been prepared in a specific manner i.e. by the hydrolysis of specific optically active cyanohydrins.

The recrystallization of such impure optically active α-hydroxycarboxylic acids is performed in an aromatic hydrocarbon and optionally in the presence of a cosolvent, thereby simultaneously improving the optical purity of α-hydroxycarboxylic acids in this simple way, without a great loss of yield, as is evident from the examples of this application at page 9 et seq.

It was surprising to achieve this objective merely by a crystallization step in an aromatic hydrocarbon.

6. ISSUES

The issues on appeal are:

1) The propriety of the rejection of claims 11-14, 16-21 and 23 under 35 U.S.C. 103(a) as being unpatentable over Effenberger et al (US 4,859,784) and further in view of Collet et al. and further in view of McMasters and

2) The propriety of the rejection of claim 22 under 35 U.S.C. 103(a) as being unpatentable over Effenberger et al. and Collet et al. and McMasters as applied to claims 11-14, 16-21 and 23 above, and further in view of Bryker et al. (US 4,983,771).

7. GROUPING OF CLAIMS

Claims 11-14 and 18-22 stand or fall together.

Claims 16 and 17 stand or fall together.

Claim 23 stands or falls separately from the remaining claims.

8. ARGUMENT

The object of the present invention is, as stated above, to find a method of simultaneously increasing the chemical and the optical purity of (*R*)- and (*S*)- α-hydroxycarboxylic acids, i.e. optically active α-hydroxy acids, which were obtained by enzyme-catalyzed addition of a cyanide group to an aldehyde or ketone with subsequent acidic hydrolysis.

The enzymatic addition of a cyanide group to an aldehyde or ketone to produce the optically active impure starting materials i.e. (*R*)- and (*S*)- cyanohydrins is not the inventive step but rather is known, as described in the present specification at page 2, lines 29 to 34.

Also the acidic hydrolysis of these cyanohydrins to produce the corresponding hydroxycarboxylic acids is also not the inventive step, but is known as described in the specification at page 3, line 38 to page 4, line 6.

The present invention resides in the specific recrystallization of these hydroxycarboxylic acids, obtained by these two known steps, which leads to an increase in optical as well as in chemical purity thereof.

Effenberger teaches the enzymatic addition of HCN to an aldehyde or ketone using D-oxynitrilase to form the corresponding cyanohydrin.

While Effenberger suggests that the crude nitrile solution can be directly subjected to the hydrolysis step in order to obtain the corresponding optically active 2-hydroxycarboxylic acid (see column 3, lines 12-19), the formation of impure or crude optically active α-hydroxycarboxylic acids is merely the starting point of the present invention.

The crucial point of the present invention is to increase the chemical purity as well as the optical purity of the crude optically active α- or 2-hydroxycarboxylic acids of Effenberger.

To overcome this deficiency, the rejection relies on Collet.

Collet discloses on page 3332, right column, next to last and last paragraph, a process for the synthesis of racemic (not optically active) substituted mandelic acid, and **not**, as stated by the final rejection, optically pure acids.

Further Collet discloses the acidic hydrolysis of racemic halomandelonitriles to the corresponding racemic substituted mandelic acids, which then must be reacted with (-)ephedrine to form the diastereomeric (optically active) salt. This salt has to be decomposed with an acid, for instance with HCl, and be recrystallized to yield the optically enriched and pure acid. **No ee-value (optical purity) is disclosed and no chemical purity is cited.**

There is absolutely no disclosure or suggestion in the Collet reference that the chemical as well as the optical purity of already optically enriched hydroxycarboxylic acids could be increased by the recited recrystallization in an aromatic hydrocarbon as claimed herein.

No art-skilled person could conclude from the Collet reference that recrystallization would have the effect of improving the optical purity as well as the chemical purity of the desired optically active hydroxycarboxylic acids, since there is absolutely no suggestion in the Collet reference that a single recrystallization step, as presently claimed, could improve the optical purity as well as the chemical one.

Further there is absolutely no suggestion in the Collet reference that the recrystallization (in order to improve the chemical and the optical purity) could be directly carried out in the hydrolysis medium as claimed in claim 16 (and 17).

Further the present process is also not obvious over the combined references (Effenberger and Collet), since neither of these references discloses or suggests that the optical and chemical purity of optically active α-hydroxycarboxylic acids, obtained by acidic hydrolysis of optically active nitriles, could be improved by a single recrystallization step using aromatic hydrocarbons, optionally with a co-solvent and none of them discloses or suggests that the hydrolysis solution obtained by acidic hydrolysis can be treated directly with aromatic hydrocarbons, optionally with a co-solvent as claimed in claim 16.

McMasters teaches a conventional recrystallization process, but McMasters does not disclose or suggest in any way that the special recrystallization as claimed herein could increase the chemical as well as the optical purity of already optically enriched hydroxycarboxylic acids.

On page 2, 2nd paragraph, McMasters discloses that if no single solvent is found suitable, then a mixed solvent recrystallization is in order.

According to the present method, however, the claimed solvents are also suitable to increase the chemical as well as the optical purity of already optically enriched hydroxycarboxylic acids, even if used alone.

Further McMasters discloses that for mixed solvent recrystallization, the substance should be relatively soluble in one solvent and relatively insoluble in another solvent. This is not true for the cosolvents used herein.

The hydroxycarboxylic acids are also relatively soluble in the co-solvents used herein, therefore, they are used to increase the solubility of the acids in the organic phase, as disclosed in the specification on page 4, lines 18 to 20.

The addition of the co-solvent herein has further the advantage that the optically purity can be further increased compared to the use of a single solvent, as can be seen from Example 3.

All of these aspects are neither disclosed nor suggested by the combined reference teachings.

In sum, from the facts discussed above, the presently claimed special recrystallization step could not have been obvious to an art-skilled person, since firstly Effenberger only discloses the enzymatic addition step and the hydrolysis step; secondly there is absolutely no disclosure or suggestion in the Collet reference that the chemical as well as the optical purity of already optically enriched hydroxycarboxylic acids could be increased by the special recrystallization step as claimed herein and further, McMasters neither discloses nor suggests that the chemical as well as the optical purity of already optically enriched hydroxycarboxylic acids could be increased by the special recrystallization step as claimed herein.

Lastly, there is absolutely no suggestion in any of the references that the recrystallization (in order to improve the chemical and the optical purity) could be directly carried out in the hydrolysis medium as claimed in claim 16 (and 17).

Claim 22 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Effenberger et al and Collet et al and McMasters as applied to claims 11 to 14, 16 to 21 and 23 above, and further in view of Bryker et al (US 4,983,771).

This rejection is also respectfully traversed.

Bryker discloses that mandelic acid, which is used as resolving agent for recovering optically pure phenyethylamine, can be recovered from the reaction mixture by extracting with MIBK.

There is absolutely no suggestion or disclosure that the optical purity of already optically enriched hydroxycarboxylic acids could be increased by the special recrystallization step in aromatic as claimed herein.

Further, it is apparent that Bryker cannot overcome the deficiencies of the above-discussed references.

In reply to Applicants' previous argument that Collet only teaches the formation of racemic mandelic acid derivatives, the Examiner replies that this material is then resolved to give optically pure compounds after recrystallization from benzene.

In reply, page 3333 of Collet reacts racemic o-chloromandelic with (-)ephedrine to enhance optical activity and this material is then crystallized from benzene. However, no such reaction with (-)ephedrine is required in the present case and, in fact, such is excluded by the "consisting essentially of" terminology of claim 23.

In fact, all of the claims in this application do not contemplate the use of (-)ephedrine to enhance optical purity since the hydroxyacids being recrystallized are already optically active.

To conclude, there is absolutely no disclosure or suggestion in the cited references that both optical and chemical purity can be improved in this simple step by recrystallization from an aromatic hydrocarbon.

Note the excellent improvement in an optical purity (as well as chemical purity) in the examples.

Even if it were apparent that the chemical purity would improve by recrystallization in aromatic hydrocarbon, there is absolutely no reasonable expectation that optical purity could be improved.

For the foregoing reasons, reversal of the final rejection is respectfully requested.

This brief is submitted in triplicate with the requisite fee of $320.00.

Respectfully submitted,

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9. APPENDIX - Claims on Appeal

11. A process for the preparation of optically and chemically highly pure *(R)*- and *(S)*-α-hydroxycarboxylic acids, which comprises recrystallizing impure *(R)*- and *(S)*-α-hydroxycarboxylic acids, prepared by acidic hydrolysis of the *(R)*- and *(S)*-cyanohydrins obtained by enzyme-catalyzed addition of a cyanide group to the corresponding aldehydes or ketones, in an aromatic hydrocarbon, optionally in the presence of a cosolvent, and obtaining optically and chemically highly pure *(R)*- and *(S)*-α-hydroxycarboxylic acids having an optical purity of over 98%ee.

12. The process as claimed in claim 11, wherein the impure *(R)*- and *(S)*-α-hydroxycarboxylic acids are prepared by acidic hydrolysis of the *(R)*- and *(S)*-cyanohydrins obtained by enzyme-catalyzed addition of a cyanide group donor to the corresponding optionally substituted aliphatic, aromatic or heteroaromatic aldehydes or ketones.

13. The process as claimed in claim 11, wherein impure, aromatic *(R)*- and *(S)*-α-hydroxycarboxylic acids of the formula $Ar\text{-}(CH_2)_nCH(OH)CO_2H$ in which n is 0 or an integer from 1 to 5 and Ar is an aryl or heteroaryl radical which is unsubstituted or mono- or polysubstituted by OH, C_1-C_4-alkyl or -alkoxy, thioalkyl, halogen, optionally substituted phenyl or phenoxy, amino or nitro, are employed.

14. The process as claimed in claim 11, wherein impure *(R)*-2-chloromandelic acid is employed as the impure *(R)*-α-hydroxyacid.

16. A process for the preparation of chemically and optically highly pure *(R)*- and *(S)*-α-hydroxycarboxylic acids, which comprises treating the hydrolysis solution obtained by acidic hydrolysis of the *(R)*- and *(S)*-cyanohydrins, prepared by enzyme-catalyzed addition of a cyanide group donor to the corresponding aldehydes or ketones, directly with an aromatic hydrocarbon, optionally in combination with a cosolvent, then extracting the mixture at hydrolysis temperature,

whereupon after cooling of the organic phase the corresponding chemically and optically highly pure *(R)*- and *(S)*-α-hydroxycarboxylic acids having an optical purity of over 98%ee crystallize out.

17. The process as claimed in claim 16, wherein chemically and optically highly pure aromatic *(R)*- and *(S)*-α-hydroxycarboxylic acids of the formula Ar-$(CH_2)_nCH(OH)CO_2H$ in which n is 0 or an integer from 1 to 5 and Ar is an aryl or heteroaryl radical which is unsubstituted or substituted by OH, C_1-C_4-alkyl or alkoxy, thioalkyl, halogen, optionally substituted phenyl or phenoxy, amino or nitro, are prepared.

18. The process as claimed in claim 11 or 16, wherein toluene, xylene, benzene, ethylbenzene, isopropylbenzene or chlorobenzenes are employed as aromatic hydrocarbons.

19. The process as claimed in claim 11 or 16, wherein the cosolvent employed is a solvent which increases the solubility of the hydroxycarboxylic acid in the organic phase and which is separable by distillation, in an amount from 5 to 50% by volume.

20. The process as claimed in claim 19 in which the co-solvent is an ether or ketone.

21. The process as claimed in claim 20 wherein the ether is tetrahydrofuran, methyl tert-butyl ether or dimethoxyethane.

22. The process according to claim 20 wherein the ketone is methylisobutyl ketone.

23. A process for the preparation of optically and chemically highly pure *(R)*- and *(S)*-α-hydroxycarboxylic acids, which consists essentially of recrystallizing impure *(R)*- and *(S)*-α-hydroxycarboxylic acids, prepared by acidic hydrolysis of the *(R)*- and *(S)*-cyanohydrins obtained by enzyme-catalyzed addition of a cyanide group to the corresponding aldehydes or ketones, in an aromatic hydrocarbon, optionally in the presence of a co-solvent, to form an organic phase and

wherein the co-solvent increases the solubility of the hydroxycarboxylic acids in said organic phase, and obtaining optically and chemically highly pure *(R)*- and *(S)*-α-hydroxycarboxylic acids having an optical purity of over 98%ee.